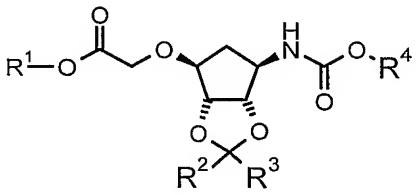
CHEMICAL PROCESS

The present invention concerns a process for the preparation of alkoxycarbonylmethoxy cyclopentanes which are useful intermediates in the preparation of pharmaceutically active triazolo[4,5-*d*]pyrimidine cyclopentanes.

The compound [1*S*-(1α, 2α, 3β (1*S**,2*R**),5β)]-3-[7-[2-(3,4-difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol (Compound A), and similar such compounds, are disclosed in WO 00/34283 and WO 99/05143. These compounds are disclosed as P_{2T} (which is now usually referred to as P_2Y_{12}) receptor antagonists. Such antagonists can be used as, *inter alia*, inhibitors of platelet activation, aggregation or degranulation.

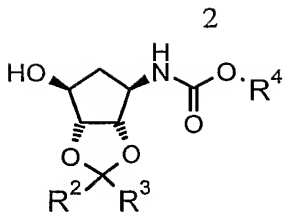
Compounds of formula (I) (see below) are useful in the preparation of Compound A (see example 1 of WO 01/92263). The preparation of a compound of formula (I) is disclosed in example 1 of WO 01/92263 and in that example the process was conducted at 0°C. It has been found that when scaling up the process of example 1 of WO 01/92263 (say to more than 0.2 mole scale) and keeping the temperature at 0°C, competing side-reactions lead to a significant increase in the level of impurities, an increase in the reagent requirement, and a resulting reduction in the percentage yield of compound of fomula (I). This is clearly a problem as it makes the process more costly and less efficient. We have now unexpectedly found that when the process is operated on a 0.2 mole scale or more, the use of a lower temperature allows the compound of formula (I) to be produced in good yield and minimizes the products of the unwanted side reactions.

The present invention provides a process for the preparation of a compound of formula (I):



(I)

wherein R^1 is C_{1-6} alkyl; R^2 and R^3 are, independently, C_{1-6} alkyl; and R^4 is C_{1-6} alkyl (such as tert-butyl) or benzyl (wherein the phenyl ring of benzyl is optionally substituted by nitro, $S(O)_2(C_{1-4}$ alkyl), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)(C_{1-4}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, CF_3 or OCF_3); the process comprising reacting a compound of formula (II):



(II)

wherein R^2, R^3 and R^4 are as defined above, with a suitable base; and reacting the product so formed with $R^1OC(O)CH_2X$, wherein R^1 is as defined above and X is chloro, bromo or iodo; wherein the process is carried out in a suitable solvent at a temperature in the range -40°C to -5°C; and wherein at least 0.2 moles of the compound of formula (II) are used in the process.

Alkyl groups and moieties are straight or branched chain and comprise, for example, 1 to 6 (such as 1 to 4) carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

In one particular aspect the present invention provides a process wherein R^1 is C_{1-4} alkyl (for example ethyl).

In another aspect the present invention provides a process wherein R^2 and R^3 are, independently, C_{1-4} alkyl; for example R^2 and R^3 are both methyl.

In a further aspect of the invention R^4 is benzyl (wherein the phenyl ring of benzyl is optionally substituted by C_{1-4} alkyl); for example R^4 is unsubstituted benzyl.

In a still further aspect the present invention provides a process wherein X is bromo.

Suitable bases include an alkali metal C_{1-6} alkoxide (for example potassium tert-butoxide).

In another aspect of the invention the molar ratio of suitable base: $R^1O_2CCH_2X$: compound of formula (II) is (1 to 1.3):(1 to 1.3):1, for example (1.1 to 1.3):(1.1 to 1.3):1, such as about 1.2:1.2:1.

Suitable solvents include cyclic and aliphatic ethers (such as tetrahydrofuran, diethyl ether, diisopropyl ether or methyl tert-butyl ether) and aromatic solvents (such as benzene, toluene or a xylene). The solvent can be a mixture of two or more solvents (for example a mixture of an ether and an aromatic solvent, as exemplified above). In another aspect the invention provides a process wherein an ether, as exemplified above, is used as solvent.

In yet another aspect of the invention the temperature is in the range -30°C to -10°C, for example -25°C to -15°C.

In a further aspect the process of the present invention comprises adding a solution of suitable base to a solution of a compound of formula (II) at -15 to -25°C, and then adding to

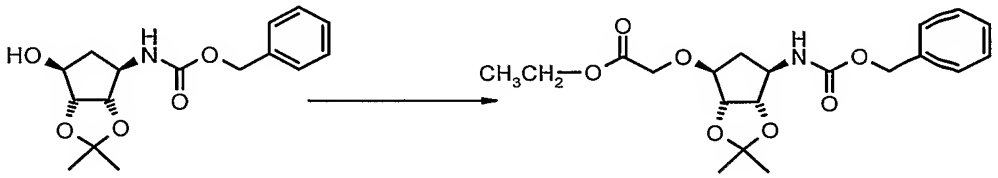
this mixture a solution of $R^1OC(O)CH_2X$ at -15 to -25°C, a suitable ether being used as solvent.

A compound of formula (II) can be prepared by a method, or a method analogous to a method, disclosed in the literature (for example WO 01/92263).

The following Example illustrates the invention.

EXAMPLE 1

This Example illustrates a process for the preparation of [3aS-(3aα,4α,6α,6aα)]-[2,2-dimethyl-6-((ethoxycarbonyl)methoxy)-tetrahydro-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester.



A solution (Solution A) of [3aS-(3aα,4α,6α,6aα)]-[tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester (80g, 260 mmol) in THF (160ml), under a nitrogen atmosphere, was cooled to –22°C. A solution of potassium tert-butoxide (36.1g, 312 mmol) in THF was prepared and added to the cooled Solution A over a period of 30 minutes, while maintaing the reaction temperature at about –20°C. This provided a reaction mixture.

A pre-made solution of ethyl bromoacetate (53.2g, 312 mmol) in THF was then added to the reaction mixture over a period of 30 minutes while maintaining the reaction temperature at about –20°C. The resulting mixture was stirred for approximately an hour at –22°C. HPLC analysis showed that there was a 98% conversion to the desired product.

Table below shows variations on this process.

Ex	Mole ratios of reagents to (II)		t-BuOK Addition		EtBrAc Addition		Hold time (min.)
	t-BuOK	EtBrAc	Time (min.)	Temp. (°C)	Time (min.)	Temp. (°C)	
2	1.40	1.46	13	-20	34	-20	23
3	1.15	1.15	22	-22	42	-22	20

Ex	Mole ratios of reagents to (II)		t-BuOK Addition		EtBrAc Addition		Hold time (min.)
	t-BuOK	EtBrAc	Time (min.)	Temp. (°C)	Time (min.)	Temp. (°C)	
4	1.20	1.20	30	-20	45	-20	15
5	1.10	1.10	20	-30	30	-30	20
6	1.20	1.20	20	-22	30	-22	20
7	1.10	1.10	20	-10	30	-10	20
8*	1.20	1.20	20	-22	30	-22	20
9	1.20	1.20	30	-22	180	-22	150
10	1.20	1.20	25	-21	45	-21	10
11	1.20	1.20	30	-22	40	-20	10
12	1.2	1.2	13	-23/-28	10	-22/-28	30
13	1.15	1.15	12	-20/-22	15	-19/-24	30

Ex = Example number

(II) = [3aS-(3aα,4α,6α,6aα)]-[tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester

t-BuOK = potassium tert-butoxide

EtBrAc = ethyl bromoacetate

* = Both the THF solution of compound of formula (II) and potassium *tert*-butoxide were filtered before use